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Abstract: INTRODUCTION Among acute coronary syndromes (ACS), ST-segment elevation myocardial infarction (STEMI) has the most severe early clinical course. Recent randomized clinical trials have demonstrated that novel antithrombotic therapies improve in-hospital outcomes in STEMI patients. We aimed to describe the effectiveness and safety of P2Y₁₂ receptor inhibitors in clinical practice in patients with STEMI based on data from contemporary European ACS registries. METHODS AND RESULTS Five registries from the PIRAEUS initiative (AAPCI/ADPAT, ALKK-PIC, AMIS Plus, Belgium STEMI, EYESHOT) provided data for the assessment of P2Y₁₂ receptor inhibitor-based dual antiplatelet therapy. Registries were heterogeneous in terms of setting, patient characteristics and treatment selection. Matched pair analysis and propensity score matching were used to assess all-cause in-hospital death rates based on data from 25'250 patients (8'577 patients on prasugrel, 5'995 on ticagrelor, and 10'678 on clopidogrel). The odds ratio for death of any cause when compared to clopidogrel were 0.72 (CI 0.62 - 0.84, $p < 0.001$) in favor of the new P2Y₁₂ receptor inhibitors (prasugrel and ticagrelor combined). In the comparison between prasugrel and ticagrelor, there were no relevant differences (OR 0.97; CI 0.77 -1.23, $p = 0.81$). Event rates of cardiovascular death and stroke were also substantially lower for the new P2Y₁₂ receptor inhibitors. The differences between clopidogrel and prasugrel or ticagrelor on major bleeding were numerically in the same order as for death of any cause, but were not statistically significant. No differences in ischemic and bleeding outcomes were observed between prasugrel and ticagrelor. CONCLUSION This analysis suggests that the prasugrel or ticagrelor compared to clopidogrel have favorable outcomes in clinical practice while not being inferior in terms of safety.

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Comparison of P₂Y₁₂ receptor inhibitors in patients with ST-elevation myocardial infarction in clinical practice: a propensity score analysis of five contemporary European registries

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Aims

Among acute coronary syndromes (ACS), ST-segment elevation myocardial infarction (STEMI) has the most severe early clinical course. Recent randomized clinical trials have demonstrated that novel antithrombotic therapies improve in-hospital outcomes in STEMI patients. We aimed to describe the effectiveness and safety of P₂Y₁₂ receptor inhibitors in clinical practice in patients with STEMI based on data from contemporary European ACS registries.

Methods and results

Five registries from the PIRAEUS initiative (AAPCI/ADPAT, ALKK-PIC, AMIS Plus, Belgium STEMI, and EYESHOT) provided data for the assessment of P₂Y₁₂ receptor inhibitor-based dual antiplatelet therapy. Registries were heterogeneous in terms of setting, patient characteristics, and treatment selection. Matched pair analysis and propensity score matching were used to assess all-cause in-hospital death rates based on data from 25 250 patients (8577 patients on prasugrel, 5995 on ticagrelor, and 10 678 on clopidogrel). The odds ratio (OR) for the death of any cause when compared with clopidogrel was 0.72 [95% confidence interval (CI) 0.62–0.84, *P* < 0.001] in favour of the new P₂Y₁₂ receptor inhibitors (prasugrel and ticagrelor combined). In the comparison between prasugrel and ticagrelor, there were no relevant differences (OR 0.97, 95% CI 0.77–1.23; *P* = 0.81). Event rates of cardiovascular death and stroke were also substantially lower for the new P₂Y₁₂ receptor inhibitors. The differences between clopidogrel and prasugrel or ticagrelor on major bleeding were numerically in the same order as for death of any cause but were not statistically significant. No differences in ischaemic and bleeding outcomes were observed between prasugrel and ticagrelor.

Conclusion

This analysis suggests that the prasugrel or ticagrelor compared with clopidogrel have favourable outcomes in clinical practice while not being inferior in terms of safety.

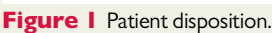
Keywords

Effectiveness • Safety • Acute coronary syndromes • ST-segment elevation myocardial infarction • Antiplatelet agents • P₂Y₁₂ receptor inhibitors • Clopidogrel • Prasugrel • Ticagrelor • Propensity score matching • Real-world evidence

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ST-elevation MI characteristics and pre-treatment are shown in *Table 2*. The STEMI location was slightly more often in the inferior artery (range 49.8–57.4%) compared with the anterior (41.6–44.3%). Killip Class I prevailed (66.4–85.7%). Chronic pre-treatment was

Table 1 Baseline characteristics: risk factors and comorbidities

Registry acronym	AAPCI/ADAPT	ALKK	AMIS Plus	BELGIUM	EYESHOT
Patient number, <i>n</i>	13 916	3553	10 224	7794	1066
Year of enrollment, <i>n</i> (%)	13 916	3553	10 224	7794	1066
Before 2009	1640 (11.8)	104 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
2010	1359 (9.8)	1061 (29.9)	0 (0.0)	0 (0.0)	0 (0.0)
2011	1889 (13.6)	1284 (36.1)	1461 (14.3)	0 (0.0)	0 (0.0)
2012	1822 (13.1)	1104 (31.1)	1786 (17.5)	0 (0.0)	0 (0.0)
2013	1770 (12.7)	0 (0.0)	1966 (19.2)	0 (0.0)	844 (79.2)
2014	1392 (10.0)	0 (0.0)	1837 (18.0)	1133 (14.5)	222 (20.8)
2015	1393 (10.0)	0 (0.0)	1499 (14.7)	2685 (34.4)	0 (0.0)
2016	1137 (8.2)	0 (0.0)	1202 (11.8)	2482 (31.8)	0 (0.0)
After 2017	1514 (10.9)	0 (0.0)	473 (4.6)	1494 (19.2)	0 (0.0)
Age (years), mean (SD)	62.5 (13.1)	62.7 (13.0)	64.2 (12.8)	63.3 (13.1)	66.0 (13.1)
Age >75 years, <i>n</i> (%)	2860/13 916 (20.6)	754/3553 (21.2)	2352/10 224 (23.0)	1718/7794 (22.0)	308/1066 (28.9)
Risk factors and comorbidities, <i>n</i> (%)					
Males	10 177/13 916 (73.1)	2641/3553 (74.3)	7770/10 224 (76.0)	5891/7766 (75.9)	767/1066 (72.0)
Diabetes mellitus	2065/11 875 (17.4)	746/3330 (22.4)	1659/9799 (16.9)	1269/7717 (16.4)	223/1041 (21.4)
Heart failure	284/2108 (13.5)	387/3521 (11.0)	147/8880 (1.7)	NA	13/1064 (1.2)
Atrial fibrillation	971/10 949 (8.9)	77/1048 (7.3)	343/9077 (3.8)	NA	NA
Prior myocardial infarction	1294/12 766 (10.1)	688/3422 (20.1)	1220/9998 (12.2)	1200/7714 (15.6)	121/1058 (11.4)
Previous stroke/TIA	394/12 155 (3.2)	140/3290 (4.3)	386/10 027 (3.8)	NA	56/1056 (5.3)
Previous PCI	1642/12 956 (12.7)	533/3457 (15.4)	1328/10 000 (13.3)	NA	107/1063 (10.1)
Previous CABG	NA	125/3508 (3.6)	281/10 000 (2.8)	NA	24/1064 (2.3)
Arterial hypertension	1395/3528 (39.5)	2232/3150 (70.9)	5407/9750 (55.5)	3673/7719 (47.6)	620/1029 (60.3)
Peripheral arterial disease	122/3528 (3.5)	159/3252 (4.9)	380/10 027 (3.8)	552/7710 (7.2)	93/1019 (9.1)
Hypercholesterolaemia	1093/3528 (31.0)	1283/2768 (46.4)	5453/9261 (58.9)	3813/7160 (53.3)	381/921 (41.4)
Current smoking	5461/12 467 (43.8)	1457/3040 (47.9)	4124/9171 (45.0)	2974/7169 (41.5)	405/1053 (38.5)
Chronic kidney disease	2050/11 834 (17.3)	373/3285 (11.4)	455/10 028 (4.5)	607/7158 (8.5)	90/1036 (8.7)

Percentages are based on the total number of patients excluding missing and unknown data. For BELGIUM, prior MI includes prior PCI and CABG. CKD is defined as either serum creatinine >1.5 mg/dL or eGFR <60 mL/m². For AAPCI-ADAPT, prior PCI includes prior CABG. CABG, coronary artery bypass grafting; NA, not applicable; TIA, transient ischaemic attack.

reported for ASA in 20.0–28.7%, clopidogrel in 3.1–10.9%, prasugrel in 0.6–4.4%, and P₂Y₁₂ overall in 3.8–15.4%. Chronic pre-treatment with anticoagulation was noted in 3.8–11.6%.

Information on the timing and in-hospital management are given in [Supplementary material online, Table S1](#). The timing from first medical contact to PCI was 79–101 min. Coronary angiography was performed in 94.0–100.0%.

Pre-cath and in-cath lab treatment are presented in [Supplementary material online, Table S2](#). The information on pre-cath lab treatment was available for AAPCI/ADPAT, AMIS Plus, and EYESHOT. In these registries, ASA was given in 77.0–96.6%, clopidogrel in 28.8–46.7%, prasugrel in 18.0–21.9%, and ticagrelor in 16.7–24.5%. In-cath lab treatment was available for AAPCI/ADAPT, ALKK, and EYESHOT. Acetylic salicylic acid was routinely used in ALKK (93.0%), and rarely in EYESHOT (13.0%) and AAPCI/ADAPT (0.1%). Clopidogrel use ranged between 10.8% and 60.2%, prasugrel between 8.8% and 43.5%, and ticagrelor between 2.1% and 20.6%.

Table 3 displays discharge treatments, which were based on ASA (96.9–99.3%), and also included clopidogrel (10.7–48.1%), prasugrel (24.4–31.3%), and ticagrelor (20.6–64.9%).

Data on in-hospital events are presented in [Table 3](#) bottom. Data on death were available in all registries and ranged from 3.5% to 7%, data on CV death from AAPCI/ADAPT, AMIS Plus, and EYESHOT ranging from 1.9% to 3.5%. Stroke/TIA was reported in 0.3–0.8%. Information on bleeding, depending on the definition, was heterogeneous: fatal bleeding as reported in AMIS Plus and EYESHOT was 0.1% each, TIMI major bleeding in AAPCI/ADPAT and EYESHOT was 0.9% and 1.3%. Urgent revascularization in AAPCI/ADPAT and EYESHOT was 0.8% and 1.1%, respectively.

Event analysis before matching patients

Baseline patient characteristics in all registries before matching patients were widely different between new P₂Y₁₂ receptor inhibitor (prasugrel and ticagrelor combined) and clopidogrel. After matching patients, these imbalances were largely improved and the standardized differences in most of the patient characteristics in each registry were within 10% ([Supplementary material online, Tables S1-1–S1-4 and S2-1–S2-4](#)). It was not possible to match patients in ALKK-PCI for Analysis 2 due to small number of patients who received ticagrelor.

Table 2 Information on STEMI at admission and pre-treatment

Registry acronym	AAPCI/ADAPT	ALKK	AMIS Plus	BELGIUM	EYESHOT
Patient number, <i>n</i>	13 916	3553	10 224	7794	1066
Admission					
Rhythm at ECG, <i>n</i> (%)	12 318		9077	.	1053
Sinus rhythm	11 098 (90.1)	NA	8310 (91.6)	NA	980 (93.1)
Atrial fibrillation	945 (7.7)	NA	343 (3.8)	NA	56 (5.3)
Others	275 (2.2)	NA	424 (4.7)	NA	17 (1.6)
STEMI location, <i>n</i> (%)	13 914	.	10 178	7747	1066
Inferior	6935 (49.8)	NA	5291 (52.0)	4449 (57.4)	584 (54.8)
Anterior	6166 (44.3)	NA	4288 (42.1)	3224 (41.6)	467 (43.8)
Undetermined	813 (5.8)	NA	599 (5.9)	74 (1.0)	15 (1.4)
Killip class, <i>n</i> (%)	10 801	.	10 164	7681	1031
I	7176 (66.4)	NA	8706 (85.7)	6246 (81.3)	811 (78.7)
II	2123 (19.7)	NA	722 (7.1)	662 (8.6)	151 (14.6)
III	616 (5.7)	NA	238 (2.3)	214 (2.8)	31 (3.0)
IV	886 (8.2)	NA	498 (4.9)	559 (7.3)	38 (3.7)
Killip class >2, <i>n</i> (%)	1502/10 801 (13.9)	NA	736/10 164 (7.2)	773/7681 (10.1)	69/1031 (6.7)
Pre-treatment, <i>n</i> (%)					
Chronic ASA	579/2893 (20.0)	520/2276 (22.8)	2466/8595 (28.7)	NA	243/1048 (23.2)
Chronic clopidogrel	88/2864 (3.1)	389/3553 (10.9)	359/8462 (4.2)	NA	35/1055 (3.3)
Chronic prasugrel	17/2899 (0.6)	156/3553 (4.4)	77/8423 (0.9)	NA	4/1056 (0.4)
Chronic ticagrelor	10/2815 (0.4)	1/1069 (0.1)	64/6972 (0.9)	NA	8/1057 (0.8)
Chronic P ₂ Y ₁₂ receptor inhibitor	115/3026 (3.8)	546/3553 (15.4)	499/8489 (5.9)	NA	47/1057 (4.4)
Chronic oral anticoagulation	110/2862 (3.8)	46/1104 (4.2)	1015/8719 (11.6)	NA	33/1057 (3.1)
Vital sign					
SBP					
<i>n</i>	10 626		9864	4090	1066
Mean (SD)	133.0 (29.2)	NA	131.8 (27.6)	131.0 (30.7)	130.6 (25.2)
DBP					
<i>n</i>	10 386		9851	4110	1066
Mean (SD)	78.4 (16.5)	NA	78.3 (17.0)	78.1 (20.7)	76.5 (14.8)
HR					
<i>n</i>	10 584		9825		1066
Mean (SD)	78.5 (19.3)	NA	78.5 (18.4)	NA	79.1 (19.0)

Percentages are based on the total number of patients excluding missing and unknown data. For vital signs, extreme data with <10 or >300 were excluded. For STEMI location, lateral, inferolateral, and posterior are merged into 'inferior'. Antero-lateral is merged into 'anterior'.

Before matching patients, the overall cumulative event rates of new P₂Y₁₂ receptor inhibitor, prasugrel, ticagrelor, and clopidogrel on in-hospital events were 3.2%, 2.6%, 3.9%, and 6.3% on death, 1.5%, 1.3%, 1.7%, and 4.5% on CV death, 0.4%, 0.3%, 0.6%, and 0.8% on stroke/TIA, and 0.4%, 0.4%, 0.4%, and 0.8% on any major bleedings, respectively.

Event analysis after matching procedure

Figure 2 presents in-hospital events, by single events, differentiated by new P₂Y₁₂ receptor inhibitor vs. clopidogrel as administered as pre-cath or in-cath lab treatment with matched population. As a consistent finding, the event rates appeared substantially lower with the new P₂Y₁₂ receptor inhibitors (with an exception for any major bleeding with low event rates). The ORs of the new P₂Y₁₂ receptor inhibitors for the death of any cause, CV death, stroke/TIA, and any major bleeding when compared with clopidogrel were 0.72 (95% CI 0.62–

0.84, $P < 0.001$), 0.70 (95% CI 0.52–0.96, $P = 0.026$), 0.52 (95% CI 0.33–0.80, $P = 0.003$), and 0.81 (95% CI 0.53–1.24, $P = 0.335$), respectively.

The standardized differences for all covariates in the matched patients were <10% after integrating registries (Supplementary material online, Tables S1–5 and S2–5).

Upon further differentiation, event rates of prasugrel and ticagrelor appeared similar across registries (Analysis 2; Figure 3). In the comparison between prasugrel and ticagrelor, there were no significant differences on any event.

Discussion

The present analysis of contemporary European real-world registries suggests that in STEMI patients the newer P₂Y₁₂ receptor inhibitors

Table 3 Discharge treatment and events in-hospital and within 30 days after discharge in propensity-matched populations

Registry acronym	AAPCI/ADAPT	ALKK	AMIS Plus	BELGIUM	EYESHOT
Patient number, <i>n</i>	13 916	3553	10 224	7794	1066
Discharge treatment, <i>n</i> (%)					
ASA	13 347/13 437 (99.3)	NA	9629/9801 (98.2)	NA	993/1025 (96.9)
Clopidogrel	6102/12 680 (48.1)	NA	2424/9770 (24.8)	654/6114 (10.7)	350/1025 (34.1)
Prasugrel	3969/12 679 (31.3)	NA	4268/9767 (43.7)	1489/6114 (24.4)	267/1025 (26.0)
Ticagrelor	2608/12 665 (20.6)	NA	2797/8691 (32.2)	3971/6114 (64.9)	353/1025 (34.4)
Oral anticoagulation	214/2714 (7.9)	NA	650/9720 (6.7)	NA	48/1025 (4.7)
In-hospital events, <i>n</i> (%)					
Death	805/13 916 (5.8)	124/3553 (3.5)	416/10 224 (4.1)	531/7613 (7.0)	41/1066 (3.8)
Cardiovascular death	111/3528 (3.1)	NA	195/10 204 (1.9)	NA	37/1066 (3.5)
Stroke/TIA	74/13 848 (0.5)	11/3553 (0.3)	70/10 224 (0.7)	NA	9/1066 (0.8)
ICH	31/13 916 (0.2)	NA	2/358 (0.6)	NA	0/1066 (0.0)
Fatal bleeding	NA	NA	10/9850 (0.1)	NA	1/1066 (0.1)
TIMI major bleeding	131/13 916 (0.9)	NA	NA	NA	14/1066 (1.3)
Any major bleeding	131/13 916 (0.9)	NA	12/9850 (0.1)	NA	14/1066 (1.3)
TIMI minor bleeding	40/3528 (1.1)	NA	NA	NA	24/1066 (2.3)
Urgent revascularization	28/3463 (0.8)	NA	NA	NA	12/1066 (1.1)
Events within 30 days after discharge, <i>n</i> (%)					
Death	NA	NA	NA	196/3264 (6.0)	NA
Cardiovascular death	NA	NA	NA	NA	NA
Stroke/TIA	NA	NA	NA	NA	NA
ICH	NA	NA	NA	NA	NA
Fatal bleeding	NA	NA	NA	NA	NA
TIMI major bleeding	NA	NA	NA	NA	NA
Any major bleeding	NA	NA	NA	NA	NA
TIMI minor bleeding	NA	NA	NA	NA	NA
Urgent revascularization	NA	NA	NA	NA	NA

ICH: intracranial haemorrhage.

Percentages are based on the total number of patients excluding missing and unknown data. Other events within 30 days after discharge except for death are not available in all registries. Any major bleeding includes ICH, fatal bleeding, and TIMI major bleeding.

compared with clopidogrel have more favourable in-hospital outcomes, while not being inferior in terms of safety.

With respect to the setting, the majority of registries, including ALKK and APCI focused on selected (tertiary) hospitals, while others were open to all types of hospitals (AMIS Plus). Thus, the considerable differences in outcomes between the registries are likely explained by their designs. Overall across all analysed registries, however, in-hospital mortality rates associated with STEMI were quite low and homogeneous. Reasons that might account for this finding include selection bias (fewer ill patients might have been preferentially recruited) and improved ACS management over the years.⁹ Patients in the five registries were similar in age and gender distribution. However, they differed substantially in the prevalence of comorbidities, such as arterial hypertension, diabetes mellitus, or prior MI.

Death rates, ischaemic events, and bleeding rates were overall lower than those reported in Phase III studies with P₂Y₁₂ inhibitors. Regarding individual P₂Y₁₂ inhibitors, patients on prasugrel, and, to a lesser degree, ticagrelor, had fewer ischaemic and bleeding events at all time points than clopidogrel-treated patients. These findings are

partly related to the fact that the newer agents were used in younger and less ill patients.

A thorough comparison of various P₂Y₁₂ inhibitors can be only be made in the presence of appropriate adjustment techniques reducing indication biases that registries are prone to. In line with its labelling, the registries consistently documented that prasugrel in everyday practice conditions is used in younger patients, compared with other antiplatelet agents as recommended by the ESC Guidelines.^{1,2} This age difference reflects the somewhat restricted labelling, as prasugrel is contraindicated in patients with prior TIA or stroke, and the drug is generally not recommended in elderly patients (≥75 years), although maintenance dose adaptation (5 mg instead of 10 mg) may be considered in such patients.¹⁰ According to the product labelling, ticagrelor should be used with caution in patients with a history of asthma and/or chronic obstructive pulmonary disease (due to a relatively high incidence of dyspnoea) and also in patients with renal impairment (due to creatinine level increases).¹¹ These side effects have not been systematically assessed in the registries contributing to PIRAEUS.

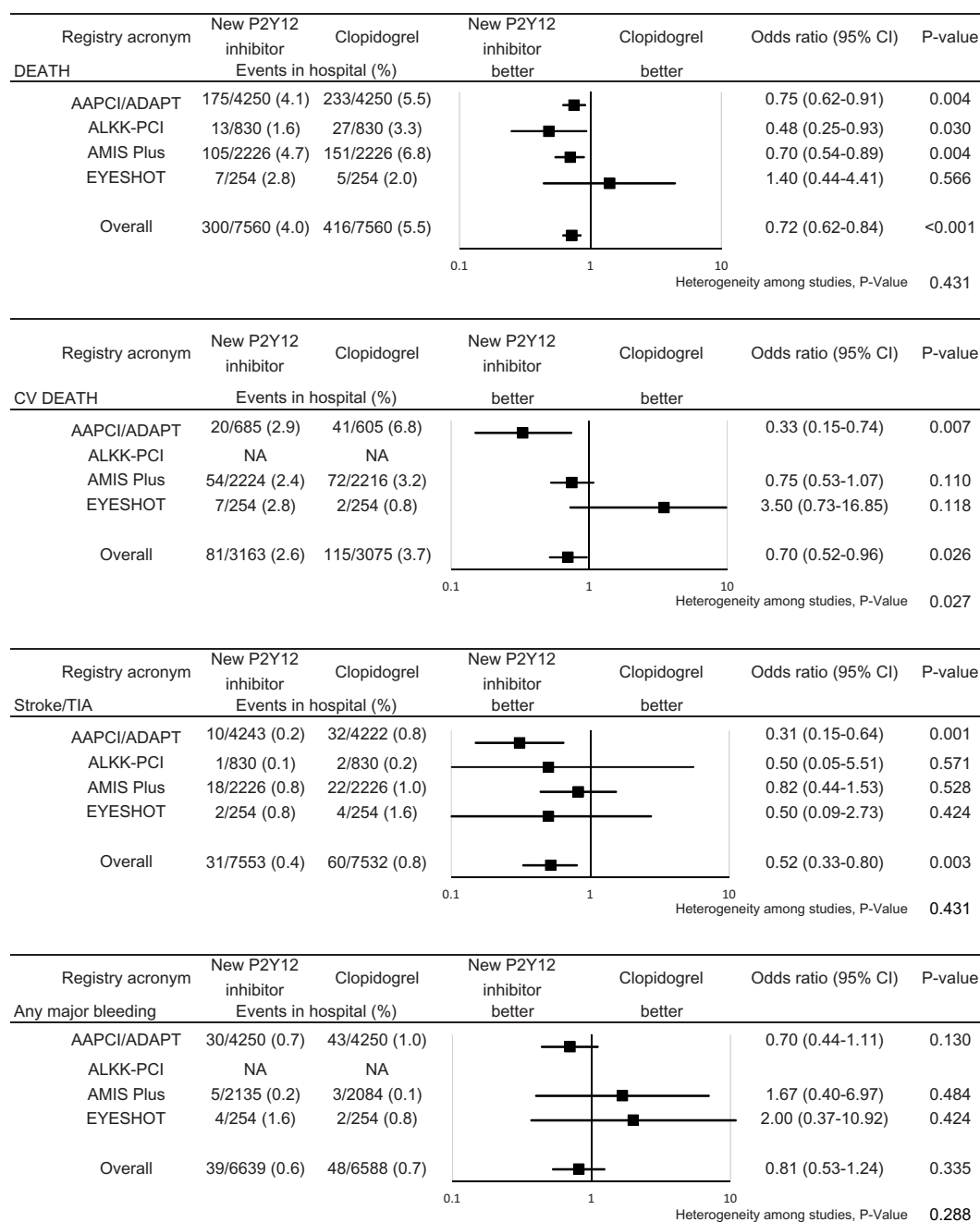


Figure 2 Relationship between the type of P₂Y₁₂ treatment and events in-hospital in propensity-matched populations (Analysis 1).

Trials comparing clopidogrel with either prasugrel or ticagrelor found a superior effectiveness of the novel antiplatelet agents,^{12,13} even in STEMI patients.^{14,15}

Prior studies have compared prasugrel or ticagrelor with clopidogrel also in a real-world setting, but a head-to-head comparison between the three available antiplatelet agents has never been performed. An AMIS Plus analysis using a propensity score-matched pairs analysis found significantly lower in-hospital mortality with

prasugrel (1.8%) vs. clopidogrel (3.1%).¹⁶ In MULTIPRAC, a multi-national, multicentre, prospective registry enrolling 2053 STEMI patients, after adjustment for differences in baseline characteristics (including a 10-year age difference), treatment with prasugrel was associated with a significantly lower risk of CV death than treatment with clopidogrel (OR 0.248, 95% CI 0.06–0.89; data submitted).¹⁷ In the SCAAR registry, the age difference was 2 years only, but the difference in 30-day all-cause mortality was substantial (prasugrel 2.5%

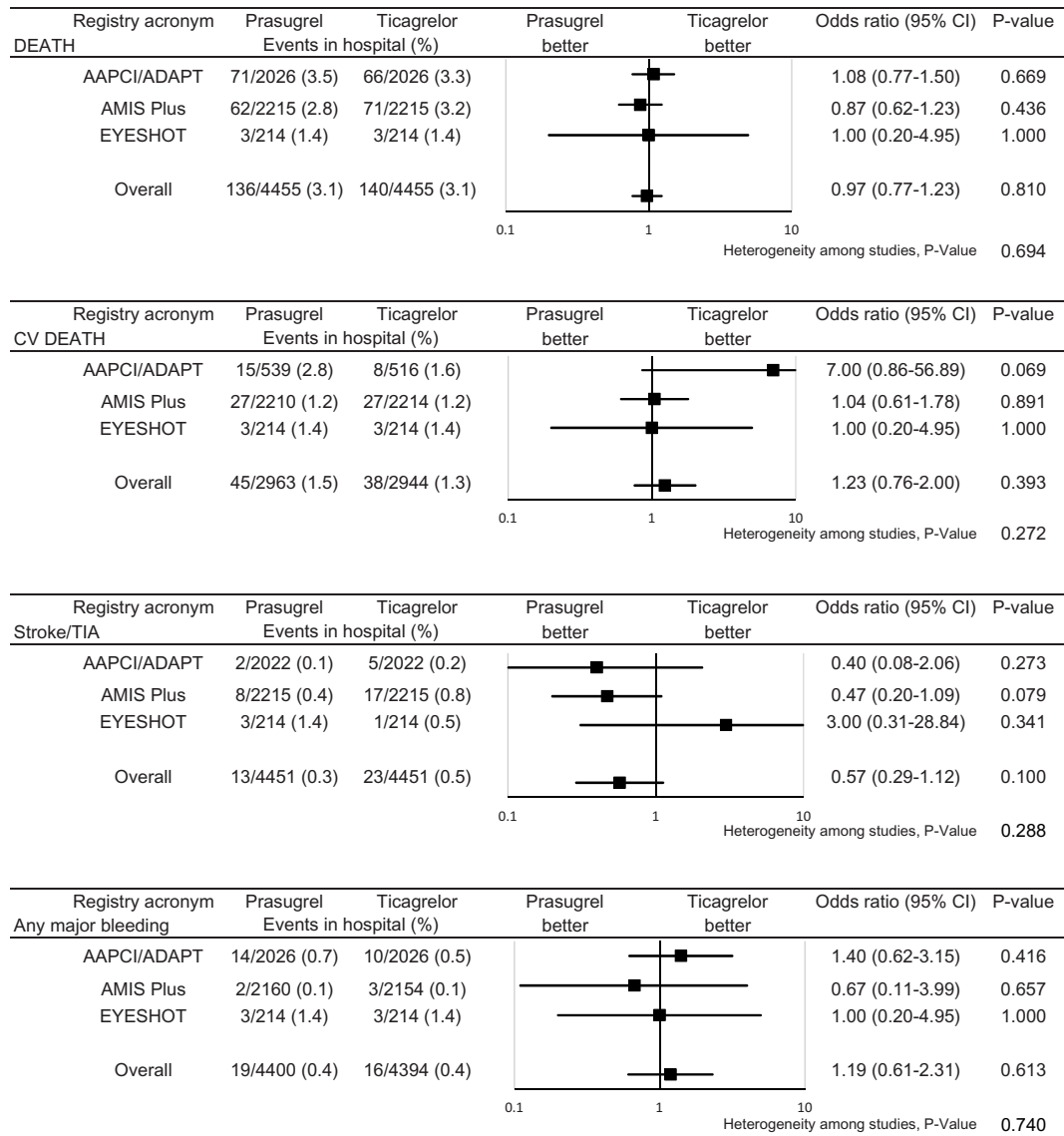


Figure 3 Relationship between the type of P₂Y₁₂ treatment and events in-hospital in propensity-matched populations (Analysis 2).

vs. clopidogrel 5.0%).¹⁸ Accordingly, a prospective cohort study of 45 073 ACS patients enrolled into the SWEDEHEART registry confirmed the results of the PLATO trial as ticagrelor was associated with a lower risk of death, MI, or stroke compared with clopidogrel [11.7 vs. 22.3%; adjusted hazard ratio (HR) 0.85, 95% CI: 0.78–0.93], as well as death alone (5.8 vs. 12.9%; adjusted HR 0.83 95% CI: 0.75–0.92).¹⁹ Re-admission for bleeding occurred more frequently with ticagrelor vs. clopidogrel (5.5 vs. 5.2%; adjusted HR 1.20, 95% CI 1.04–1.40).¹⁹

Recently, ticagrelor and prasugrel have been directly compared in the multicentre, randomized, open-label ISAR-REACT 5 trial.³ Among the 4018 patients with ACS enrolled in this trial, a primary endpoint event—death from any cause, MI, or stroke at 1 year after randomization—occurred in 9.1% of patients in the ticagrelor group

and 6.8% in the prasugrel group (HR 1.36, 95% CI: 1.09–1.70; *P* = 0.006), without any difference in terms of major bleeding events (BARC Type 3 through 5). Among the pre-specified subgroup of patients with STEMI no difference was observed in terms of primary efficacy (10.1 vs. 7.9; HR 1.31, 95% CI 0.94–1.81) and safety endpoint across all enrolled patients, including those with STEMI.³ These findings are in accordance with our real-world data showing a numerical, not significant reduction in the ischaemic event rate associated with prasugrel compared with ticagrelor, with a similar occurrence of bleeding events during the hospitalization for STEMI.

Limitations

Not all of the previously identified suitable registries⁶ provided data in the agreed structured format and several registries could,

therefore, not be analysed for the purpose of this article. Outcomes analyses were restricted to the short in-hospital period and does not allow for long-term assessment. The concurrent use of oral anticoagulation and other anticoagulants, such as unfractionated heparin, low-molecular-weight heparins, and fondaparinux, needs to be taken into account. Bleeding events were categorized using various definitions and were not standardized across registries. The low rate of bleeding complications is noteworthy, as real-life data are usually more likely to document increased safety hazards, compared with randomized controlled trials.

In conclusion, the present analysis of contemporary European registries suggests that in clinical practice STEMI patients the newer P₂Y₁₂ receptor inhibitors compared with clopidogrel have favourable in-hospital outcomes while not being inferior in terms of safety.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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